REMARKS

1. Status of the claims

Claims 1-24, as filed, are pending. Applicants acknowledge that claims 9, 10, 18 and 19 are currently under examination, and that all other claims are formally withdrawn from consideration, in order to facilitate examination. However, Applicants wish to retain their rejoinder rights to all claims capable of rejoinder, and elect to defer making any required amendments until such time as the pending claims are acknowledged to be patentable.

2. The claims as amended fulfill the requirements of 35 U.S.C. § 112, 1st ¶.

The pending claims stand rejected under 35 U.S.C. §112, first paragraph for failing to fulfill the written description requirement for the claim elements "melatonin agonists" and "compounds that increase endogenous melatonin production." The Action cites the portions of the MPEP that have incorporated the Written Description Guidelines as promulgated by the Patent and Trademark Office on January 6, 2001, as well as Federal Circuit decisions including *University of Rochester v. G.D. Searle*. Applicants respectfully traverse.

Applicants draw two distinctions with the principles recited in the Action. First, Applicants are not claiming *per se* either genera of melatonin agonists or compounds that increase endogenous melatonin production. Different considerations apply when an applicant wishes to claim a broad class of compounds as such, as opposed to a use of said compounds. In the instant case, a salient distinction is that Applicants are entitled to claim their inventive methods of using these compounds, and relevant to the extent of their disclosure is the knowledge regarding these compounds known in the art. This is in contrast to the amount of disclosure required to claim the compounds *per se*, where perforce there would be *no* knowledge of the compounds in the art. Moreover, this situation (claiming an inventive method for compounds known in the art) is distinct from the method claims in the *University of Rochester* case; that case was more analogous to instances of claiming compounds per se because there were *no* compounds known in the art that were specific COX-2 inhibitors. In the *Rochester* case the claimed methods encompassed the only known uses for the recited COX-2 inhibitors. In

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contrast, Applicants are not claiming all uses for the melatonin *et al*. but rather their specifically-claimed uses.

The instant situation is completely different. The art regarding melatonin *per se* and its agonists and compounds that could increase endogenous production of melatonin in a human was not in its infancy, as in the *Rochester* case. Further, Applicants are not claiming these compounds, and their each and every use; they are claiming the specific use(s) of compounds, examples of which are known in the art, for use in their inventive method. This is completely different from the citations provided in the Action.

Evidence of the established status in the art of such compounds includes the following:

Kräuchi et al. (1995). "Evidence for a phase advance in circadian temperature regulation after acute melatonin and a melatonin agonist (S-20098)." Sleep Research 24: 526.

Martinet et al. (1996). "Entrainment of circadian rhythms by S-20098, a melatonin agonist, is dose and plasma concentration dependent." Pharmacology Biochemistry and Behavior 54: 713-718.

Redman et al. (1995). "Dose dependent effects of S-20098, a melatonin agonist, on direction of re-entrainment of rat circadian activity rhythms." Psychopharmacology (Berl) 118(4): 385-90.

Sack RL and Lewy AJ, (1986). "Desmethylimipramine treatment increases melatonin production in humans, Biological Psychiatry 21: 406-410.

Applicants thus respectfully contend that the assertion in the Action that their pending claims do not fulfill the written description requirement are in error, and request that the Examiner withdraw this ground of rejection

Applicant believes that all grounds of rejection on 35 U.S.C. §112, first paragraph grounds have been traversed by argument, and respectfully ask the Examiner to withdraw the rejections asserted on this basis.

3. The claims as amended fulfill the requirements of 35 U.S.C. § 112, 2nd ¶.

Claim 10 stands rejected as being indefinite for reciting administration times for melatonin, melatonin agonists and compounds that increase endogenous melatonin production in a human in terms of circadian time. The purported assertion of the rejection is that circadian

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time is relative to first morning light exposure time, and thus (one supposes, since this is not explicitly stated) any particular clock time corresponding to the ranges of circadian time recited (CT18 to CT6 *vs.* CT 6 to CV18) are not unambiguously recited.

However, each individual has a dim light melatonin onset (DLMO) time where the plasma concentration of endogenous melatonin rises above 10pg/mL. This time corresponds to CT14, and thus provides an independent standard for unambiguously determining an individual's melatonin circadian rhythm. An individual can determine the expected DLMO as being 14 hours after first morning exposure to light (defined as CT0). In the case of jet lag, waketime after travel cannot be used to estimate the dim light melatonin onset time. It can be assumed that DLMO occurs 14 hours after waketime before travel and then convert that to a clock time based on the new time zone (such as adding six hours if a person has flown from NY to Paris). Moreover, if the actual waketime is unknown it can be estimated to be 7 a.m., resulting in a DLMO time of 9 p.m.; in the NY-to-Paris example considered above, DLMO will occur at 3 a.m. the first day in Paris and, if the teachings of the present invention are followed, DLMO times will advance at 3 hours per day. Entrainment to 9 p.m. will thus occur after three days and remain stable until the return to the home time zone. The present invention thus provides a way for treating jet lag based on the number of time zones and direction traveled and the individual's melatonin phase response curve (PRC). In contrast, the cited art teaches melatonin administration times that are the same (bedtime) for travel in either direction (east-west) and for any number of time zones.

The standard for determining whether a term is indefinite is whether it would be understood by those with skill in the art. The Action acknowledges that the relative "time zero" (CT0) from which the recited circadian times are calculated is known in the art (as the time of first morning light exposure); this is also explicitly set forth in Applicants' specification (in the paragraph bridging pages 18-19). Applicants respectfully submit that the features set forth in the Action attempting to support rejection based on indefiniteness would prove to the skilled worker to be precisely the opposite: rather than having to specify both clock time and relative position (longitude) in the world after travel, the melatonin et al. administration time is unambiguously determined for each individual relative to their first morning light time. Moreover, the position taken in the Action is contrary to the accumulated prosecution history of Applicants' related U.S.

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patents (Nos. 5,242,941; 5,420,152; 5,591,768; 5,716,978; 6,069,164; 6,423,738; 6,638,963; 6,794,407); it is unlikely that this objection is correct when it has not been raised in almost 17 years of Patent Office determinations that circadian time, and ranges of effects of melatonin et al. set forth in circadian time, have been an accepted way of setting forth these limitations.

Finally, Applicants respectfully contend that the term "circadian time" would be understood by those with skill in the art, that this is the only relevant measure of whether or not a term is indefinite, and by that measure the instant grounds of rejection are not supported in the art. Applicants thus request that the Examiner reconsider and withdraw rejection of claim 10 on 35 U.S.C. §112, second paragraph grounds.

4. <u>The claims are neither anticipated nor rendered obvious by the cited art.</u>

Claims 9-10 and 18-19 stand rejected under 35 U.S.C. §102(b) by the teachings of WO95/05819 to Lewy et al. The Action posits that the methods claimed herein have the same effect for the same purpose as disclosed in the earlier reference, and are thus not novel.

The cited teachings by Lewy et al. restricted the amount of melatonin administered to an individual to prevent "spillover" of exogenously administered melatonin from one portion of the melatonin PRC (such as the phase-advance portion, CT6 to CT18) to the opposite portion (the phase-delay portion, CT18 to CT6). The Lewy reference teaches that such spillover could diminish the extent of the phase-shifting effect of exogenously-added melatonin, by stimulating both portions of the PRC (albeit to different extents). For example, the phase-advancing effects of exogenous melatonin administration three hours prior to DLMO were expected to be reduced if the elevated melatonin concentrations persisted past CT18.

In contrast, the present invention teaches that higher doses of exogenous melatonin can be administered, provided that the overall melatonin levels are greater in one portion of the melatonin PRC than the other (*i.e.*, CT6-CT18 *vs.* CT18-CT6). The instantly-claimed methods have the advantage *inter alia* that melatonin can be administered in more convenient, commercially-available dosage forms. The instant methods have the further advantage that administration times are more easily determined, based on the calculation of the DLMO time as set forth above. Thus, Applicants respectfully contend that the cited reference does not teach the

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instantly-claimed invention, and Applicants respectfully request that this ground of rejection be withdrawn.

The Action also rejects the pending claims over the teachings of Short *et al*. Applicants note initially that their own prior patents asserted in the Action to claim patentably-indistinct subject matter to the pending claims have been granted over the same teachings of the Short reference asserted herein under §102. Applicants respectfully contend, as they have successfully contended in their earlier patents, that the deficiencies in appreciation of the claimed invention are even more evident with regard to the rejection over the Short reference. Short's teachings are simple: administer a soporific amount of melatonin at destination bedtime, *regardless of circadian time*. These teachings are understandable because Short was ignorant of the existence of the melatonin phase response curve identified by the present inventors. This is not merely the understanding of a mechanism of action, because said understanding changes the times of melatonin et al. administration in a way not taught by the cited reference. In order for Short to be an anticipatory reference, each and every limitation of the instant method must be taught in the reference. This is impossible for the Short reference, since the basis for determining administration times [the human melatonin phase response curve (PRC) as discovered by the inventor after publication of the Short reference] was unknown to Short. And the possibility that administering melatonin et al. according to Short might, for some travel between some time zones, encompass administration that overlaps with the times taught in the instant specification do not render the Short reference anticipatory. Inherent anticipation requires a reference to inherently follow the same method or produce the same result each and every time; the practice of the instantly-claimed methods is not possible using the Short method performed in ignorance of an individual's melatonin PRC.

The following examples illustrate the differences in melatonin administration time as taught by the inventors using the methods disclosed in this application in contrast with the teachings of the Short patents. Compared with the administration times required according to the present invention, the melatonin administration times recommended by the Short reference are typically suboptimal, questionably-effective, ineffective or simply wrong (*i.e.*, they would produce a melatonin PRC phase shift in the direction opposite to the direction needed to effect the appropriate correction in the melatonin PCR):

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Example 1. Flying two time zones to the west (normal waketime at 6 am and bedtime 10 pm):

Day before and day of travel

Melatonin PRC Time	Short (Destination Bedtime)
7 a.m. (embarkation time)	midnight (embarkation time) 10 p.m. (destination time) Both wrong according to melatonin PRC

This is a difference of 7 hours in recommended times between the Short recommended melatonin administration time and the instant invention. Also, administering melatonin at destination bedtime either before or after flying to the west coast and after flying from Chicago would be the wrong time because it would cause a phase advance, not the desired or required phase delay, when traveling west (before leaving Chicago, taking melatonin before 1 or 2 a.m. will cause a phase advance). If bedtime is 10 a.m. in Chicago, destination (west coast) bedtime while still in Chicago is midnight in Chicago. After arrival at the west coast, 10 p.m. west coast time is midnight in Chicago and is still a few hours before the phase delay responses begin.

Moreover, the present invention recommends a constant clock time of melatonin administration, at waketime (CT0 = 7 a.m.) in the days before and the day of traveling west, and CT8 (= 2 p.m.) when traveling east, regardless of the number of time zones to be crossed. In contrast, Short recommends the opposite, that is, a different clock time before travel depending on the number of time zones to be crossed, and a constant clock time (i.e., bedtime) every day after arrival at destination.

Example 2. Flying east nine time zones

Day before and day of travel (embarkation time)

Melatonin PRC time	Short (Destination Bedtime)
2 p.m.	1 p.m.

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First day after arrival (destination time)

Melatonin PRC time	Short (Destination Bedtime)
9 p.m.	10 p.m.

Second day after arrival

Melatonin PRC time	Short (Destination Bedtime)
6 p.m.	10 p.m. (suboptimal time)

Third day after arrival

Melatonin PRC time	Short (Destination Bedtime)
3 p.m.	10 p.m. (not very effective time)

Fourth day after arrival

Melatonin PRC time	Short (Destination Bedtime)
2 p.m.	10 p.m. (questionably effective time)

3. Example 3: Going west 10 time zones

Day before and day of travel (embarkation time)

Melatonin PRC time	Short (Destination Bedtime)
7 a.m.	8 a.m.

First day after arrival (destination time)

Melatonin PRC time	Short (Destination Bedtime)
9 p.m.	10 p.m.

Second day after arrival

Melatonin PRC time	Short (Destination Bedtime)
midnight	10 p.m.

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Third day after arrival

Melatonin PRC time	Short (Destination Bedtime)
7 a.m.	10 p.m. (wrong time)

Fourth day after arrival

Melatonin PRC time	Short (Destination Bedtime)
7 a.m.	10 p.m. (wrong time)

Fifth day after arrival

Melatonin PRC time	Short (Destination Bedtime)
7 a.m.	10 p.m. (wrong time)

In addition, the Short patent does not permit melatonin administration after sleep, *i.e.* after destination waketime. In contrast, the present invention permits such administration *provided that* the resulting stimulation of the melatonin PRC is in the desired direction (i.e., a phase advance or a phase delay).

Applicants respectfully contend that, contrary to the assertions in the action that the claimed invention is anticipated by either their own prior patent application or the Short reference, the claimed invention sets forth a new method for administering melatonin et al. to a human suffering from jet lag, and thus is not anticipated by these references. Applicants respectfully request that the Examiner withdraw this ground of rejection.

The claims are also rejected under 35 U.S.C. §103 as being obvious over the teachings of U.S. Patent No. 4,600,723, substantially for the same reasons used to reject the pending claims over the Short teachings in the anticipation rejection above. Applicants respectfully contend that the reason their invention is non-obvious is substantially the same: in the absence of knowledge of the human melatonin phase response curve, Short could not have rendered the instant invention obvious. Indeed, the non-obviousness of the methods as instantly claimed is even more patent, since Short teaches administration of soporific amounts of melatonin at destination bedtime, and further administration during the night as needed. Thus, Short anticipates that the melatonin administered according to his teachings would not persist to produce elevated plasma

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melatonin levels by CT0 (i.e., morning) and there are of course no teachings to this effect in the Short reference. Applicants thus respectfully contend that the Short reference cannot render obvious their invention as instantly claimed, and request that the Examiner withdraw this ground of rejection.

5. The claims are not barred under the judicially-created doctrine of obviousness-type double patenting.

The pending claims stand rejected under the judicially-created doctrine of obviousness-type double patenting over a variety of Applicants' earlier U.S. patents. Applicants respectfully contend that their own prior art does not render their claims obvious, because that art required administration of melatonin et al. at reduced dosages, so as not to result in elevated melatonin et al. levels on both the advance (CT6 to CT18) and delay (CT18 to CT6) zones (i.e., restricted elevated levels to one zone or the other but not both). The instant invention removes this dosage restriction and teaches that higher doses can be administered, *provided that* greater levels are produced in one zone than the other.

Applicants thus respectfully contend that this art could not render their instantly-claimed invention obvious, and ask the Examiner to withdraw these grounds of rejection.

CONCLUSIONS

Applicant believes that all grounds of rejection have been overcome by amendment or traversed by argument, and request that the pending claims be passed to issue.

If the Examiner in charge of this application believes it to be helpful at any time during prosecution of this application, she is invited to contact Applicants' undersigned representative by telephone at (312) 913-0001.

Respectfully submitted,
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